REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-161 were pending in this application. Claims 1-73, 106-125, 129-144, 146-155 and 157-161 were withdrawn from consideration. Claims 1-68, 106-125, 129-144, 146-155, 157-161 have been cancelled. Claims 145 and 156 have been placed in independent form with respect to cancelled claims 144 and 150, respectively, as suggested by the Office Action. Claims 69-74, 76-80, 89-91, 95, 99, 100, 105, 126-128, 145, and 156 have been amended. Claims 162-202 have been added to clarify and round out the scope of the instant invention. Support for the amendments and new claims can be found throughout the specification, figures, and original claims. Accordingly, claims **69-105, 126-128, 145, 156, 162-202** are now pending in this application.

It is respectfully asserted that no new matter is added by these amendments or new claims.

The Examiner is thanked for rejoining claims of Group VIII (75-78, 79 and 105) and XVI (156) with the elected claims of Group VII (74, 78-105, 126-128 and 145). It is believed that claims 69-73 (Group VI) should also be rejoined in view of the amendments made thereto as they may be searched and examined together with the elected invention without undue burden.

Applicants appreciate the Examiner's comments relating to the claims of priority to US provisional application Serial No. 60/476,513, filed June 6, 2003, and US provisional application Serial No. 60/422,755, filed October 31, 2002. However, the issue raised by the Examiner is believed to be moot since each of the prior art references cited by the Examiner have publication dates that occur prior to the filing dates of both priority documents.

It is submitted that the claims are patentably distinct over the prior art and that these claim are and were in full compliance with the requirements of 35 USC §112. The amendments of the claims herein are not made for the purpose of patentability within the meaning of 35 USC §§ 101, 102, 103 or 112; but rather, the amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly

stated that the amendments should not give rise to any estoppel, as they are not narrowing amendments.

Any reference made herein to the present application is with respect to Paragraph Nos. of the published version of this application, namely US Publication No. 2004/0197769, which published October 7, 2004.

I. THE OBJECTION TO DECLARATION IS OVERCOME

The Office Action objects to the declaration as being defective for not identifying the citizenship of each inventor. A substitute declaration is filed herewith pursuant to 37 CFR §1.67(a) and as required by the Office Action. The substitute declaration is consistent with the requirements of 37 CFR §1.63 and now indicates the citizenship of each inventor. Accordingly, it is respectfully requested that the objection to the declaration be reconsidered and withdrawn.

II. THE REJECTIONS UNDER 35 USC §112, 2nd PARAGRAPH, ARE OVERCOME

The Office Action rejects claims 75-79, 89-91, 94, 105, 126-128, 145 and 156 under 35 USC §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejections to the above claims are based on several different grounds and are individually traversed as follows.

Claim 75 stands rejected under 35 USC §112, second paragraph, as allegedly being indefinite for reciting "WNV NS5 protein" and "E glycoprotein" within the same claim. Applicants have cancelled claim 75 without prejudice or any intention of creating estoppel while reserving the right to pursue the claim in a continuing application. The cancellation renders the rejection moot. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 75-79 are rejected under 35 USC §112, second paragraph, as allegedly being indefinite for omitting essential steps. As noted above, claim 75 has been cancelled, rendering the rejection moot. Claims 76-78 were amended to depend solely from claim 74, thereby obviating the rejections to claims 76-78, and to 79, which is dependent on claim 78. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action rejects claim 77 under 35 USC §112, second paragraph, as allegedly being indefinite for including a reference to Genbank accession number AF 404756 and for the reference to "the amino acid sequence encoded by the NS5 protein encoding DNA sequence of." Applicants appreciate the Examiner's comments with regard to these rejections. Claim 77 was amended to include reference to the relevant SEQ ID No., namely SEQ ID No. 8, and to remove

the reference to "the amino acid sequence encoded by the NS5 protein encoding DNA sequence of," thereby obviating the rejection. Accordingly, reconsideration and withdrawal of the above rejections is respectfully requested.

Claims 78, 89, and 90 stand rejected under 35 USC §112, second paragraph, as allegedly being indefinite. The Office Action contends that the claimed "fusion protein" form of the invention is incompatible with the requirement that the claimed WNV NS5 protein have a "native conformation or non-denatured structure." In particular, the Office Action argues that "[o]nce you fuse the entire protein to something else it cannot have either a native conformation or a non-denatured structure." See Office Action, page 6, lines 5-7 (emphasis added). Applicants respectfully disagree.

While it is certainly possible that a protein's three-dimensional structure could be disrupted such that it becomes denatured or loses its native conformation when constructed as a fusion protein, the Office Action's conclusion that a protein when fused to "something else" cannot have a native conformation or non-denatured structure is not consistent with the general understanding of one of ordinary skill in the art to which this application pertains.

Contrary to the Office Action, the skilled person would undoubtedly appreciate that fusions between a protein of interest and another protein or polypeptide would not necessarily cause the protein of interest to become denatured or lose its native conformation. Indeed, the widespread use of fusion proteins in the biotechnology arts (and related arts) is evidence that contradicts the Office Action's conclusion. This is especially apparent when one considers that many assays and/or experiments involving fusions require that a fused protein of interest substantially retain its normal function or activity, and necessarily, that protein's three dimensional structure.

In one common example, schemes relating to the purification of proteins commonly involved fusion proteins. In particular, a protein of interest may be fused to an affinity-tag, such as, a His-tag (other examples include maltose-binding-protein (MBP), glutathione-S-transerase (GST), thioredoxin (TRX), and avidin/streptavidin tags, each of which are taught by in the present application), which facilitates the purification of the protein through the use of chromatographic methods. In many such schemes, the function and/or activity of the protein of interest is measured or assayed during the course of the purification scheme as a way to track various information such as the concentration of the protein of interest or its location in specific

fractions. Accordingly in such cases, the fusion does not significantly disrupt the three-dimensional structure of the protein of interest since its activity is readily measurable.

In another example, fusion proteins can be used to study and/or characterize the biological function(s) of a protein of interest. In particular, one of ordinary skill in the art will be familiar with marker proteins. Marker proteins, such as enzymes like LacZ or fluorescent proteins such as Green Fluorescent Protein, may be fused to a protein of interest in order to assess various characteristics of that protein of interest, such as its expression level, its tissue-specificity, or even its intracellular location. For example, the use of GFP-based fusions to proteins of interest is widespread. Like with affinity-tag fusions, the assays and/or experiments involving a marker fusion protein are dependent upon the protein of interest retaining its biological function and/or activity. As such, in many cases, the marker fusion does not significantly disrupt the protein of interest's three dimensional structure.

Morin et al. ("A protein trap strategy to detect GFP-tagged proteins expressed from their endogenous loci in *Drosophila*," PNAS, 98(26):15050-15055 (2001)) illustrates the point that a fusion does not necessarily result in a loss of a protein of interest's three dimensional structure. The reported study relates to the construction and expression of endogenous proteins of *Drosophila* as GFP fusions and the investigation of the subcellular distribution of the GFP fusions during development by way of confocal microscopy. A goal of the study reportedly is to accurately detect the dynamics of the spatial distribution of the GFP fusions of interest during the cell cycle and various developmental events. The reference notes the "[t]he adjunction of a GFP module at either the N- or C- terminal end of a protein usually does not significantly affect its structure and function." (See Morin et al., page 15055, attached herewith).

Similarly, Li et al. ("Integrating bioprocessing in *Saccharomyces cerevisiae* using green fluorescent protein as a fusion partner," Biotechnology and Bioengineering, 79(6):682-693 (Jul 2002)) studied the use of GFP for monitoring expression, degradation, purification, and localization of hexokinase (HXK) of *S. cerevisiae*. The study constructed a HXK-GFP fusion. The protein additionally was engineered with an enterokinase (EK) cleavage site between the HXK and GFP and a histidine tag (His-tag) at the N-terminus of the protein to allow purification by affinity chromatography. Thus, the HXK was fused to both a marker protein and an affinity tag. The study reported that the "fusion of GFP did not cause structural alteration of HXK and thus did not affect the enzymatic activity of HXK" and that the level of measured activity of

HXK was the same whether in the fusion protein form or in the non-fused form following cleavage at the EK site. (Attached herewith).

In consideration of the above examples, the Office Action's assessment that claiming WNV NS5 as a fusion protein "is incompatible with the limitation that WNV NS5 protein or immunogenic fragment thereof has a native conformation or non-denatured structure" contradicts the knowledge of one of ordinary skill in the art. In particular, the Office Action's reasoning that a protein cannot have a native conformation or a non-denatured structure once fused to "something else" respectfully is incorrect. In fact, as evidenced above, a protein of interest may indeed retain its normal biological activity and/or function when constructed as a fusion protein. Accordingly, reconsideration and withdrawal of the above rejection is respectfully requested.

Claim 90 is further rejected under 35 USC §112, second paragraph, as allegedly being indefinite for referring to "WNV NS5 or subfragment there of." The claim has been amended to recite "fragment" substituted in place of "subfragment," rendering the rejection moot. Support for this amendment may be formed throughout the specification and original claims. Thus, reconsideration and withdrawal of the above rejection is respectfully requested.

Claim 105 is rejected under 35 USC §112, second paragraph, as being indefinite for allegedly not setting forth any steps involved in the claimed "method for the transfer of information." The claim has been amended to include steps of carrying out the method for the transfer of information, rendering the rejection moot. No new matter is added by this amendment. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 126-128, 145, and 156 stand rejected under 35 USC §112, second paragraph, as allegedly being indefinite in the recitation of "rapidly detecting." Claims 145 and 156 are further rejected under 35 USC §112, second paragraph, as allegedly being indefinite for reciting the term "recent infection." The Office Action complains that the terms "rapidly" and "recent" are relative terms and that the bounds of such terms are not known. Applicants traverse as follows.

One of ordinary skill in the art would be able to ascertain and appreciate the meanings of both "rapidly detecting" and "recent infection." Applicants would first like to point out that one can find other examples of patented claims that contain the recitations "rapidly detecting" and "recent infection." For example, US Patent No. 6,465,201 claims "[a] method for rapidly detecting and enumerating microorganisms, having a level of microbial adenosine triphosphate

(ATP), in mammalian cell cultures..." And, US Patent No. 6,372,426 claims "[a] method for differentiating a recent infection from an older infection by determining the avidity of an antibody to an antigen according to the method of claim 8, wherein low avidity indicates a recent infection, and high avidity indicates an older infection." Applicants wish to make clear that reference to the above patents does not necessarily bind them to the specific definitions of "rapidly detecting" or "recent infection" that may be set forth therein. The above patents are referenced simply to demonstrate that, by patenting the claims, the USPTO has taken the position that the recitations "rapidly detecting" and "recent infection" are not indefinite and their meaning can be understood by one of ordinary skill in the art. On the basis of these prior patents, Reconsideration and withdrawal of the above rejection is respectfully requested.

Moreover, MPEP 707.07(g) states in part that "[c]ertain technical rejections (e.g. negative limitations, indefiniteness) should not be made where the examiner, recognizing the limitations of the English language, is not aware of an improved mode of definition." It is presumed that the Examiner is aware of the effects of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.* on patent prosecution, *i.e.* **any** amendment related to patentability can be viewed as prosecution history estoppel. In this environment, Applicants' representative cannot in good faith modify the claims on behalf of their clients if there are no reasons of record to support the rejection. Even if the applicants were amenable to modifying the claim, they cannot afford to guess at what the examiner would find to be permissible terminology. With this in mind, section 2173.02 of the MPEP is reproduced below:

> The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, ***not whether more suitable language or modes of expression are available.*** When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. ***Examiners are encouraged to suggest claim language to applicants to improve clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.*** (see MPEP 2173.02) (emphasis added)

Here, the terms "rapidly detecting" and "recent infection" define the claimed subject matter with a "reasonable degree of particularity and distinctness." One of ordinary skill in the

art would appreciate the meaning of such terms based on their ordinary meanings and in context of the specification as a whole. Thus, "[s]ome latitute in the manner of expression and aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire." Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 91, 94, and 126-128 are rejected under 35 USC §112, second paragraph, as allegedly being indefinite for the recitation "increase reaction kinetics." The Office Action asserts that the term "increase" is a relative term and therefore it is indefinite. With the aim of moving prosecution forward, the recitation "increased reaction kinetics" has been removed from independent claims 91 and 126. Claims 127 and 128 are now drafted in dependent form from claim 126. Dependent claim 94 was amended to "enhance reaction kinetics." This limitation was also added to new dependent claim 187 (depends from claim 126). Claims 91 and 187 further include the recitation of temperature, time, and motion. Support for "enhance reaction kinetics" can be found throughout the specification and figures, and in particular at Paragraph 188 of the published version of the present application. There, "enhanced reaction kinetics" is defined as "an antibody-antigen binding reaction that occurs at a rate that exceeds the expected reaction rate when carried out under conditions used in prior art methods." One of ordinary skill in the art would certainly appreciate the reaction rates characteristic of prior art methods. Accordingly, reconsideration and withdrawal of the present rejection is requested.

III. THE REJECTIONS UNDER 35 USC §112, 1ST PARAGRAPH, ARE OVERCOME

The Office Action rejects claims 74-104, 126-128, 145 and 156 under 35 USC §112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office Action contends that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. According to the Office Action, the rejection involves the following six aspects: I. "not detectably cross-reactive," II. "against a flavivirus other than WNV," III. "protective immune response," IV. "having native conformation or non-denatured structure," V. use of NS5 to detect flavivirus infection, and VI. other Section 112 first paragraph issues. Applicants respectfully disagree and traverse as follows.

I. "not detectably cross-reactive"

The Office Action rejects claim 74 for lack of enablement with respect to the recitation that the claimed WNV NS5 protein "is specifically reactive with anti-WNV antibodies but **not detectably cross-reactive** with antibodies against a flavivirus other than WNV." (emphasis as indicted in Office Action). The Office Action also notes that claims 75, 80, 91, 99, 126, 127, and 128 use similar language. Applicants respectfully disagree with this rejection. One of ordinary skill in the art would certainly appreciate the meaning of "not detectably cross-reactive," especially in the context of the specification, figures, and original claims. However, in the interest of moving prosecution forward, claims 74, 75, 80, 91, 99, 126, 127, and 128 have been amended to recite that the WNV NS5 protein "is specifically reactive with anti-WNV antibodies but not substantially ~~detectably~~ cross-reactive with antibodies against a flavivirus other than WNV," thereby rendering the rejection moot. Support for the amendment can be found throughout the specification, for example at Paragraphs 5, 7, 67, 146 and 147 of the published application, and based on the cross-reactivity data depicted in Figures 26, 27, and 29. Accordingly, reconsideration and withdrawal of the above rejection is respectfully requested.

II. "against a flavivirus other than WNV"

The Office Action rejects claims 74-104, 126-128 and 145 for lack of enablement as to the recitation "against a flavivirus other than WNV" and contends that the specification does not enable the skilled person to use the invention commensurate in scope with the claims. Contrary to the Office Action, the language "against a flavivirus other than WNV" is enabled throughout the specification, for example, at Paragraphs 75, 76, and 78 of the published application and in the original filed claims. However, with the aim of advancing prosecution forward, the rejected claims were amended to recite that the claimed WNV NS5 is not substantially cross-reactive with antibodies "against JEV, SLEV, or DENV," thereby rendering the rejection moot. Support for this amendment can be found throughout the specification, figures, and examples, for instance, at Paragraphs 5, 7, 60, and 156 of the published application. Accordingly, reconsideration and withdrawal of the rejection based on the above second aspect is respectfully requested.

III. "protective immune response"

Claim 75 is rejected for lack of enablement as to the recitations "[a] method for detecting a protective immune response in a subject..." and an NS5 that is "specifically reactive with

protective antibodies against WNV..." As noted above, claim 75 has been cancelled and claims 77 and 78 have been amended to no longer depend from claim 75. Claim 75 is cancelled without prejudice or any intention of creating any estoppel as to equivalents and Applicants reserve the right to pursue claim 75 in a continuing application. The rejection based on claim 75 is thus rendered moot. Reconsideration and withdrawal of the rejection is respectfully requested.

IV. "having native conformation or non-denatured structure"

Claims 74, 75, 80, 91, 99, 126, 127, 128, and 145 (when rewritten by incorporating the limitations of withdrawn claim 144) stand rejected under 35 USC §112, first paragraph, for allegedly lacking enablement with respect to the recitation "where the WNV NS5 protein or the immunogenic fragment thereof having a native conformation or non-denatured structure..." More in particular, the Office Action seems to contend that undue experimentation would be required to enable the claimed immunogenic fragments of WNV NS5 due to, *inter alia*, an alleged lack of guidance and working examples. Applicants respectfully disagree and traverse as follows.

First, claim 75 was cancelled. And, claim 127 and 128 were amended to depend from claim 126. Also, the prior-pending claims including 91, 99, 126, and 145 did not recite the "immunogenic fragment thereof" language. Accordingly, the rejection to these claims is obviated. Reconsideration and withdrawal of the rejection to claims 75, 91, 99, 126, 127, 128, and 145 is respectfully requested.

Second, claims 74 and 80 were amended to move the recitation "immunogenic fragment thereof" into dependent claims 164 and 170, respectively. The recitation is also now present in new dependent claims 175, 181, 191, and 199 and in currently amended claim 71. The Examiner's rejection is further traversed as follows.

It is respectfully submitted that the Office Action's argument is not completely understandable because it is not apparent what relevance the cited medical dictionary definition has to do with the present invention. One of ordinary skill in the art to which the present application pertains would appreciate that the term "denatured" relates to the state of a protein's three dimensional structure and consequently a protein's function or activity. For example, it is widely understood that a hard-boiled egg is comprised of denatured egg protein formed as a result of the heating process used to prepare the egg. Confusingly, the Office Action cites the medical dictionary definition "made unnatural or changed from the normal in any of its

characteristics." This definition of "denatured" does not reflect the meaning of that term as would be understood by one of ordinary skill in the art. Consider, for example, a protein variant that differs from its natural, 'wildtype' protein by only 1 or 2 amino acid residues and where the substituted amino acids do not affect the biological function or activity of the protein. Such a protein would meet the Office Action's definition of "denatured" because the amino acid substitutions constitute a change from the normal in any of its characteristics (changed primary structure). However, this conclusion would be contrary to the meaning of "denatured" as it would be understood by the ordinarily skilled artisan. Accordingly, it is respectfully submitted that the Office Action's argument is consequently unclear.

Notwithstanding the referenced definition of "denatured" referred to in the Office Action, undue experimentation would not be required to enable the claimed immunogenic fragments of WNV NS5. According to the Court of Appeals for the Federal Circuit in *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988),

> [e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation. The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Id. at 1404.

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands*. For example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Applying *Wands* to the instant facts, it is clear that enablement exists, to wit, *inter alia*, that the quantity of experimentation necessary is low; the amount of direction or guidance

presented is high; and the relative skill of those in the art is high. Indeed one has to look no further than to WO 02/072036, which is incorporated by reference in its entirety in the present application, in order to appreciate that the making of immunogenic fragments is completely within the purview of one of ordinary skill in the art. For instance, Example 6 of WO 02/0172036 outlines a method for making fragments of WNV proteins and then testing them using assays that would be understood by one of ordinary skill in the art. There, three-dimensional modeling of WNV E protein was performed against a known flavivirus E protein structure to identify candidate peptides for testing a vaccine, i.e. peptides as immunogenic fragments of WNV E protein. To determine the immunogenicity of the fragments, sera from WNV-infected mice were tested for the presence of antibodies specific for the peptides. At least one peptide was determined to react specifically against anti-WNV antibodies. One of ordinary skill in the art would be able to follow the methods of WO 02/072036—or other similar and/or appropriate method—and, in connection with the methods of the present invention, be able to obtain the claimed immunogenic fragments of NS5. Consequently, as undue experimentation does not exist, the assertion in the Office Action that the instant application does not provide enablement for the immunogenic fragments of WNV NS5 is, therefore, misplaced.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

V. use of NS5 to detect flavivirus infection

Claim 156 stands rejected for lack of enablement for being directed to a method for carrying out an immunochromatographic test for rapidly detecting a flavivirus infection in an animal. Applicants respectfully disagree with the Office Action. Detection of a flavivirus infection using WNV antigens is supported throughout the specification. However, with the goal of moving prosecution forward, claim 156 has been amended to clarify the claimed invention. As such, the claim is directed to detecting a "WNV infection" and utilizes WNV NS5 antigens. Also, claim 156 has been amended to include the limitations of its cancelled independent claim, namely claim 150. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

VI. other Section 112 first paragraph issues

The Office Action rejects claim 76 under 35 USC §112, first paragraph, for lack of enablement with respect to the recitation of "NS5 protein or fragment thereof is from WNV isolate 2741." To round out the scope of the claimed invention and to comply with the

Examiner's remarks, claim 76 has been amended to recite "wherein said NS5 protein is encoded by nucleic acid positions 7,633 – 10,377 of SEQ ID NO. 1" No new matter is added by this amendment. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

IV. THE REJECTION UNDER 35 USC §101 IS OVERCOME

The Office Action rejects claim 105 under 35 USC §101 based on the reason that a method is claimed without setting forth any steps, which "results in a claim which is not a proper process claim under 35 USC §101." Claim 105 has been amended to include steps of the claimed method, thereby rendering the rejection moot. Reconsideration and withdrawal of the rejection is respectfully requested.

V. THE REJECTIONS UNDER 35 USC §103 ARE OVERCOME

Claims 74, 76-82, 85-90 and 126-128 are rejected under 35 USC §103(a) as allegedly being *prima facie* obvious over Wang et al. ("Wang") in view of Valdes et al. ("Valdes").

To establish a *prima facie* case of obviousness, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. There must also be a reasonable expectation of success. Further still, the prior art reference alone or in combination must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully submit that the claims under rejection are not prima facie obvious over Wang in view of Valdes since, *inter alia*, there lacks any motivation or suggestion to combine the references. Further, Wang and Valdes, either alone or in combination, fail to teach or suggest each of the elements of the present invention.

Wang relates to a method of detecting a WNV infection in an animal. More in particular, Wang relates to the preparation of and testing of recombinant forms of WNV E, M and NS1 antigens against sera obtained from horses known to be infected with WNV. The reference utilizes immunoblots to assess the performance of each of the antigens in the serodiagnosis of WNV infections. Valdes relates to a method of characterizing the immune response to DENV structural and nonstructural proteins. In particular, Valdes tests sera from DENV fever patients and DENV hemorrhagic fever patients against DENV-2 and DENV-4 antigens E, NS1, NS3, and NS5 using Western blotting procedures.

It is respectfully submitted that neither the references themselves nor the knowledge of persons of ordinary skill in the art provide any motivation or suggestion to combine the references. In fact, Applicants assert that the references teach away from their combination. And, "[i]t is improper to combine references where the references teach away from their combination." See MPEP 2145 (citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983)).

More in particular, Wang reports that the WNV E protein is immunodominant and that "[a]ntibodies to the M protein or NS1 protein were not detected by immunoblot in all 10 West Nile virus-infected horses or six humans with West Nile virus." (See page 107 of Wang). Thus, although the WNV E protein detected WNV-infected horse and human sera, neither M or NS1 detected any sera. Given Wang's data that WNV E was "immunodominant" against the tested sera while WNV M nor NS1 were non-reactive, and given that nonstructural proteins (like NS1 or NS5) would generally be regarded by the ordinarily skilled person as less immunogenic than a viral structural protein (like E), Wang would not be suggestive to the skilled artisan that NS5, another nonstructural protein, would likely be a good candidate to detect a WNV infection with specificity and without substantial cross-reactivity to other flaviruses, especially JEV, DENV, and SLEV. Thus, Wang would in fact teach away from the present invention. Thus, the combination with Valdes and Wang would not be proper.

Further, the Office Action appears to suggest that it would be obvious to try the present invention, starting with the teachings of Wang and modifying Wang with the use of the NS5 protein of Valdes to reach the inventive method of, *inter alia*, detecting a WNV infection using a substantially purified WNV NS5 protein having a native conformation or nondenatured structure. In light of Wang which shows that a nonstructural protein is a poor antigen to use to detect WNV-infected sera, and in view of the fact that Valdes relates to an entirely different virus, namely DENV, at best, it would have been "obvious to try" combining the references. The Examiner, however, is reminded that "obvious to try" is not the standard under 35 USC §103. *In re Fine*, 5 USPQ 2d 1596, 1599 (Fed. Cir. 1988). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. See MPEP 2143.01. It is respectfully submitted that neither Wang nor Valdes provides the requisite suggestion or desirability to be combined to reach each and every element of the invention.

Further, to establish *prima facie* obviousness of a claimed invention, each of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974); also MPEP 2143.03. It is respectfully submitted that neither Wang nor Valdes, either alone or in combination, teaches nor suggests each and every element of claimed invention. For example, neither reference teaches or suggests a method for detecting a WNV infection in a subject by contacting a biological sample with a substantially purified NS5 protein or an immunogenic fragment thereof having a native conformation or non-denatured structure whereby the NS5 protein is specifically reactive with anti-WNV antibodies but not substantially cross reactive with antibodies against JEV, SLEV, or DENV. For example, Wang relates to the use of WNV E protein to detect a WNV infection, whereas the present invention relates, *inter alia*, to the use of WNV NS5 in a method to detect a WNV infection. And, surely Wang does not teach a WNV NS5 that has a native conformation or non-denatured structure and that is specifically cross-reactive with anti-WNV antibodies but not substantially cross reactive with other flaviviruses, especially JEV, SLEV, and DENV.

Valdes relates to analyzing the antibody response to DENV infected sera, including the response to DENV E, NS1, NS3, and NS5 antigens. Contrary to Valdes, the instantly claimed invention relates to detecting WNV infections, not DENV infections. Although DENV and WNV are related flaviviruses, it would not have been obvious to extend the results of Valdes to modify , especially in view of the inconsistent data and lack of data presented in Valdes. For example, the reactivity of NS3 from DENV-2 and DENV-4 is completely different and NS5 is tested for only a single DENV type (see Table 1). Valdes does not correct for the deficiencies in Wang, and vice versa. Neither Wang nor Valdes, either alone or in combination, teach a method for the detection of a WNV infection in a subject suspected of having said infection that includes the step of contacting a biological sample from the subject with an isolated and substantially purified polypeptide comprising a WNV NS5 protein having a native conformation or non-denatured structure whereby the NS5 protein or the immunogenic fragment thereof is specifically reactive with anti-WNV antibodies but not substantially cross-reactive with antibodies against JEV, SLEV, or DENV.

Accordingly, in view of the preceding comments, reconsideration and withdrawal of the 35 USC §103 rejection in view of Wang and Valdes is respectfully requested.

The Office Action also rejects claims 82-84, 91-104, 145 and 156 as being unpatentable over Wang in view of Valdes and in further view of Mandy. It has already been explained that the present invention is patentable over Wang and Valdes, either alone or in combination. Mandy clearly does not correct for the deficiencies of Wang and Valdes as outlined above. While Mandy relates to the technique of microsphere immunoassays, it does not teach each and every element of the presently claimed invention. For example, Mandy does not teach a method for the detection of a WNV infection in a subject suspected of having said infection that includes the step of contacting a biological sample from the subject with an isolated and substantially purified polypeptide comprising a WNV NS5 protein or an immunogenic fragment thereof having a native conformation or non-denatured structure whereby the NS5 protein or the immunogenic fragment thereof is specifically reactive with anti-WNV antibodies but not substantially cross-reactive with antibodies against JEV, SLEV, or DENV.

Accordingly, reconsideration and withdrawal of the 35 USC §103 rejection in view of Wang, Valdes, and Mandy is respectfully requested.

Moreover, each of the above 35 USC §103(a) rejections is traversed on the ground that Wang is not a prior art document. The attached Declaration Under 37 C.F.R. § 1.132 (hereinafter "Declaration") states that Wang is not the work of others as defined by 35 USC §102(a). The Declaration is sufficient to overcome the grounds of rejection of claims 74, 76-82, 85-90 and 126-128 as obvious over Wang in view of Valdes and of claims 82-84, 91-104, 145 and 156 as obvious over Wang, Valdes and in further view of Mandy because the Declaration clearly states that T. Wang, L.A. Magnarelli, J.F. Anderson, L.H. Gould, S.L. Bushmich, and E. Fikrig did not make an independent inventive contribution to the invention claimed in this application.

Reconsideration and withdrawal of the rejection under 35 USC § 103 is respectfully requested.

VI. DOUBLE PATENTING IS HELD IN ABEYANCE

The Office Action provisionally rejects claims 74-105, 126-128, 145 and 156 under judicially created doctrine of double patenting over claims 1-9, 13-21, 24-35 and 56-57 of copending Application No. 10/839,442.

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

VII. REQUEST FOR INTERVIEW

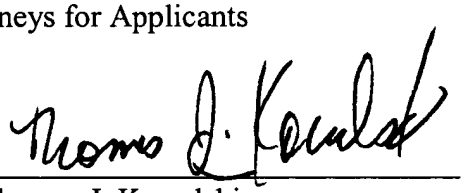
If any issue remains as an impediment to allowance, an interview with the Examiner is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

VIII. CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application, reconsideration and withdrawal of the rejections of and objections to the application, and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: 

Thomas J. Kowalski
Reg. No. 32,147
(212) 588-0800